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WALKER, Ann, Louie [GB/GB], GlaxoSmithKline,
Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY
(GB).

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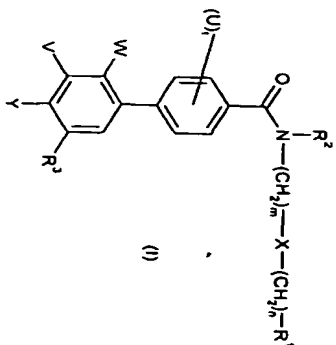
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0124933.3(71) Applicant (for all designated States except US): GLAXO
GROUP LIMITED [GB/GB], Glaxo Wellcome House,
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(54) Title: BIPIHENYLCARBOXYLIC AMIDE DERIVATIVES AS P38 KINASE INHIBITORS

(57) Abstract: Compounds of formula (I), or pharmaceutically ac-
ceptable salts or solvates thereof, and their use as pharmaceuticals,
particularly as p38 kinase inhibitors.

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optionally substituted by one or more R^8 groups and heteroaryl wherein the heteroaryl may be optionally substituted by one or more R^8 groups:

R^8 is selected from $C_{1-6}alkyl$, $C_{1-6}alkoxy$, halogen, trifluoromethyl and $-NR^9R^{10}$, or R^8 and R^9 , together with the carbon atoms to which they are bound, form a

five- or six-membered saturated or unsaturated ring to give a fused bicyclic ring system, wherein the ring that is formed by R^8 and R^9 may optionally contain one or two heteroatoms selected from oxygen, nitrogen and sulfur.

R^7 is selected from hydrogen, $C_{1-6}alkyl$ and phenyl wherein the phenyl group may be optionally substituted by one or more R^8 groups:

R^8 is selected from hydrogen and $C_{1-6}alkyl$;

or R^7 and R^8 , together with the nitrogen atom to which they are bound, form a five- to six-membered heterocyclic ring optionally containing one additional heteroatom selected from oxygen, sulfur and N- R^8 , wherein the ring may be substituted by up to two $C_{1-6}alkyl$ groups:

R^8 is selected from hydrogen and methyl;

R^9 is selected from hydrogen, $C_{1-6}alkyl$ and $-(CH_2)_4-C_3-cycloalkyl$ optionally substituted by $C_{1-6}alkyl$;

R^{10} is selected from hydrogen and $C_{1-6}alkyl$;

or R^9 and R^{10} , together with the nitrogen atom to which they are bound, form a three- to seven-membered heterocyclic ring optionally containing one additional heteroatom selected from oxygen, sulfur and nitrogen, wherein the ring may contain up to one double bond and the ring may be substituted by one or more R^{11} groups:

R^{11} is selected from $C_{1-6}alkyl$, oxy , $-CH_2OC_{1-6}alkyl$, trichloromethyl and $-N(C_{1-6}alkyl)_2$;

U is selected from methyl and halogen;

W is selected from methyl and chlorine;

V and Y are each selected independently from hydrogen, methyl and halogen;

m and n are independently selected from 0, 1 and 2, wherein each carbon atom of the resulting carbon chain may be optionally substituted with up to two groups selected independently from $C_{1-6}alkyl$ and the sum of $m+n$ is from 0 to 4;

p, q and r are independently 0 or 1;

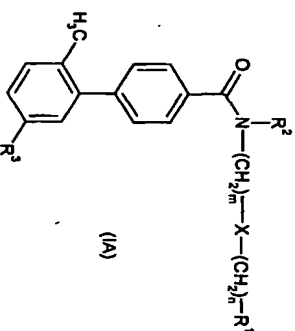
s is 0, 1, 2 or 3;

t is selected from 0, 1 and 2;

or a pharmaceutically acceptable salt or solvate thereof.

According to a further embodiment of the invention there is provided a compound of formula (IA):

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wherein R^1 , R^2 , R^3 , m, n and X are as defined above, or a pharmaceutically acceptable salt or solvate thereof.

In a preferred embodiment, the molecular weight of a compound of formula (I) does not exceed 1000, more preferably 800, even more preferably 600.

The group R^1 may be optionally substituted by up to three substituents, more preferably one or two substituents, selected from $C_{1-6}alkyl$, $C_{1-6}alkoxy$, oxy , halogen, hydroxy, $C_{1-6}alkyl$, $-N(C_{1-6}alkyl)_2$, $-CH_2N(C_{1-6}alkyl)_2$, $-CO_2C_{1-6}alkyl$, phenyl optionally substituted by halogen and benzyl optionally substituted by halogen and/or cyano.

When X is phenyl, the optional substituents for X are selected independently from $C_{1-6}alkyl$, $C_{1-6}alkoxy$, halogen, trifluoromethyl, trifluoromethoxy, and cyano. Particularly preferred substituents are methyl, chloro, fluoro, cyano, methoxy and trifluoromethoxy. X may also be optionally substituted by $C_3-cycloalkyl$.

In a preferred embodiment, when X is phenyl, R^1 is preferably an optionally substituted group selected from pyrrolidinyl, furyl, pyrrolyl, imidazolyl, imidazolidinyl, pyrazolyl, tetrazolyl, oxazolyl, oxadiazolyl, piperidinyl, piperazinyl, morpholino, pyridyl, pyrimidinyl, thienyl, benzimidazolyl and quinolyl. Particularly preferred groups are morpholino, pyrrolidinyl, imidazolyl, pyridyl, oxazolyl, oxadiazolyl, pyrazolyl, piperidinyl, piperazinyl and pyrimidinyl. The optional substituents for R^1 when X is phenyl are selected independently from $C_{1-6}alkyl$, $C_{1-6}alkoxy$, oxy , halogen, hydroxy, $C_{1-6}alkyl$, $-N(C_{1-6}alkyl)_2$ and $-CH_2N(C_{1-6}alkyl)_2$. Particularly preferred optional substituents are methyl and oxy .

In a preferred embodiment, when X is a bond, R^1 is selected from an optionally substituted pyrrolidinyl, isoxazolyl, furyl, thienyl, imidazolyl, pyrazolyl, tetrazolyl, oxazolyl, thiazolyl, oxadiazolyl, piperidinyl, piperazinyl, morpholino, pyridyl, tetrahydrofuran-2-yl, tetrahydrothiophenyl and quinolyl. Particularly preferred groups are piperazinyl, piperidinyl, morpholino, imidazolyl, thienyl and pyrrolidinyl. The optional substituents for R^1 when X is a bond are selected independently from $C_{1-6}alkyl$, $C_{1-6}alkoxy$, oxy , halogen, hydroxy, $C_{1-6}alkyl$, $-N(C_{1-6}alkyl)_2$, $-CH_2N(C_{1-6}alkyl)_2$, $-CO_2C_{1-6}alkyl$, phenyl optionally substituted by halogen and benzyl optionally substituted by halogen and/or cyano. Particularly preferred optional substituents are methyl and oxy .

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In a preferred embodiment, R² is selected from hydrogen, C₁₋₄alkyl and -CH₂-cyclopropyl, more preferably hydrogen.

In a preferred embodiment, R⁴ is selected from -(CH₂)_nphenyl optionally substituted by R⁵ and/or R⁶ and -(CH₂)_nheteroaryl optionally substituted by R⁵ and/or R⁶. In a particularly preferred embodiment, R⁴ is -(CH₂)_nheteroaryl optionally substituted by R⁵ and/or R⁶, especially furyl, thienyl, isoxazolyl or pyridyl optionally substituted by -(CH₂)_nNR⁹R¹⁰. In a preferred embodiment, R⁵ is selected from C₁₋₄alkyl, halogen, -NR⁹R¹⁰, C₃₋₅cycloalkyl, phenyl optionally substituted by one or more R⁶ groups and heteroaryl optionally substituted by one or more R⁶ groups.

In a preferred embodiment, R⁶ is selected from C₁₋₂alkyl and halogen. In a further preferred embodiment, R⁶ is -NR⁹R¹⁰. In a preferred embodiment, R⁷ is selected from hydrogen and C₁₋₄alkyl.

In a preferred embodiment, R⁸ is selected from hydrogen and C₁₋₄alkyl.

In a preferred embodiment, R⁹ is selected from hydrogen, C₁₋₄alkyl, C₃₋₅cycloalkyl and -CH₂C₃₋₅cycloalkyl.

In a preferred embodiment, R¹⁰ is selected from hydrogen and C₁₋₄alkyl.

In a preferred embodiment, R⁶ and R¹⁰, together with the nitrogen atom to which they are bound, form a five to six membered heterocyclic ring optionally containing one additional heteroatom selected from oxygen, sulfur and N-R², wherein R² is methyl, and the ring may be substituted by one or more R¹¹ groups. In a further preferred embodiment, R⁹ and R¹⁰, together with the nitrogen atom to which they are bound, form a pyrrolidiny group.

In a preferred embodiment, R¹¹ is selected from methyl and oxy.

In a preferred embodiment, W is methyl.

In a preferred embodiment, V and Y are each selected independently from hydrogen, chlorine and fluorine. In a further preferred embodiment, V is fluorine.

In a preferred embodiment, m and n are independently selected from 0, 1 and 2, and the sum of m+n is from 0-3.

In a preferred embodiment, q is 0.

In a preferred embodiment, r is 0.

In a preferred embodiment, s is selected from 0, 1 and 2.

In a preferred embodiment, t is selected from 0 and 1. In particular, t is 0.

It is to be understood that the present invention covers all combinations of particular and preferred groups described hereinabove.

Particular compounds according to the invention include those mentioned in the examples and their pharmaceutically acceptable salts and solvates. Specific examples which may be mentioned include:

N-(6-Methyl-4-((3-(4-methylpiperazin-1-yl)propylamino)carbonyl)-1,1'-biphenyl-3-yl)-2-pyrrolidin-1-ylisonicotinamide;

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N-(6-Methyl-4-((3-morpholin-1-ylpropylamino)carbonyl)-1,1'-biphenyl-3-yl)-2-pyrrolidin-1-ylisonicotinamide;

N-(4-((3-imidazol-1-ylpropylamino)carbonyl)-6-methyl-1,1'-biphenyl-3-yl)-2-pyrrolidin-1-ylisonicotinamide;

N-(6-Methyl-4-((4-methylpiperazin-1-yl)carbonyl)-1,1'-biphenyl-3-yl)-2-pyrrolidin-1-ylisonicotinamide;

N-(6-Methyl-4-((3-morpholin-4-ylmethylbenzyl)amino)carbonyl)-1,1'-biphenyl-3-yl)-3-furamide;

N-(4-(((1-(4-butoxycarbonylpiperidin-4-yl)methyl)amino)carbonyl)-6-methyl-1,1'-biphenyl-3-yl)-3-furamide; and

N-(6-Methyl-4-((2-(4-methylpiperazin-1-ylmethyl)anilino)carbonyl)-1,1'-biphenyl-3-yl)-3-furamide.

Further specific examples which may be mentioned include:

N-(6-Methyl-4-((4-(4-methylpiperazin-1-yl)benzyl)amino)carbonyl)-1,1'-biphenyl-3-yl]thiophene-3-carboxamide;

N-(6-Methyl-4-((3-(4-methylpiperazin-1-yl)methyl)phenyl)amino)carbonyl)-1,1'-biphenyl-3-yl]thiophene-3-carboxamide;

N-(6-Methyl-4-((3-(morpholin-4-ylmethyl)benzyl)amino)carbonyl)-1,1'-biphenyl-3-yl)-3-furamide; and

N-(6-Methyl-4-((4-(4-methylpiperazin-1-yl)benzyl)amino)carbonyl)-1,1'-biphenyl-3-yl]isoxazole-3-carboxamide.

As used herein, the term "alkyl" refers to straight or branched hydrocarbon chains containing the specified number of carbon atoms. For example, C₃₋₅alkyl means a straight or branched alkyl containing at least 1, and at most 5, carbon atoms. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, isobutyl, isopropyl and t-butyl. A C₁₋₄alkyl group is preferred, for example methyl, ethyl or isopropyl. The said alkyl groups may be optionally substituted with one or more halogen atoms, in particular fluorine atoms, for example, trifluoromethyl.

As used herein, the term "alkoxy" refers to a straight or branched chain alkoxy group, for example, methoxy, ethoxy, propoxy, prop-2-oxo, butoxy, but-2-oxo, 2-methylprop-1-oxo, 2-methylprop-2-oxo, pentoxy, or hexyloxy. A C₁₋₄alkoxy group is preferred, for example methoxy or ethoxy.

As used herein, the term "cycloalkyl" refers to a non-aromatic hydrocarbon ring containing the specified number of carbon atoms. For example, C₃₋₅cycloalkyl means a non-aromatic ring containing at least three, and at most seven, ring carbon atoms. Examples of "cycloalkyl" as used herein include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. A C₃₋₅ cycloalkyl group is preferred, for example cyclopropyl.

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As used herein, the terms "heteroaryl ring" and "heteroaryl" refer to a monocyclic five- to seven-membered unsaturated hydrocarbon ring containing at least one heteroatom independently selected from oxygen, nitrogen and sulfur. Preferably, the heteroaryl ring has five or six ring atoms. Examples of heteroaryl rings include, but are not limited to, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl. The said ring may be optionally substituted by one or more substituents independently selected from C₁₋₆alkyl and oxy.

As used herein, the terms "heterocyclic ring" and "heterocyclic" refer to a monocyclic three- to seven-membered saturated or non-aromatic, unsaturated hydrocarbon ring containing at least one heteroatom independently selected from oxygen, nitrogen and sulfur. Preferably, the heterocyclic ring has five or six ring atoms. Examples of heterocyclic groups include, but are not limited to, aziridinyl, pyrrolidinyl, pyrrolidinyl, imidazolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, morpholino, tetrahydropyranyl, tetrahydrofuryl, and thiomorpholino. The said ring may be optionally substituted by one or more substituents independently selected from C₁₋₆alkyl and oxy.

As used herein, the terms "fused bicyclic ring system" and "fused bicyclic" refer to a ring system comprising two five- to seven-membered saturated or unsaturated rings, the ring system containing at least one heteroatom independently selected from oxygen, nitrogen and sulfur. Preferably, each ring has five or six ring atoms. Examples of suitable fused bicyclic rings include, but are not limited to, naphthyl, indolyl, indolinyl, benzothienyl, quinolyl, isoquinolyl, tetrahydroquinolyl, benzodioxanyl, indanyl and tetrahydronaphthyl. Each ring may be optionally substituted with one or more substituents independently selected from halogen, C₁₋₆alkyl, oxy, -(CH₂)_nNR¹⁰R¹¹, -CO(CH₂)_nNR¹⁰R¹¹, and imidazolyl. Particularly preferred substituents are chlorine, imidazolyl and -CH₂-N(CH₃)₂.

As used herein, the terms "halogen" or "halo" refer to the elements fluorine, chlorine, bromine and iodine. Preferred halogens are fluorine, chlorine and bromine. A particularly preferred halogen is fluorine.

As used herein, the term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s) which occur and events that do not occur.

As used herein, the term "substituted" refers to substitution with the named substituent or substituents, multiple degrees of substitution being allowed unless otherwise stated.

As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula (I) or a salt thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include water, methanol,

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ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include water, ethanol and acetic acid. Most preferably the solvent used is water.

Certain compounds of formula (I) may exist in stereoisomeric forms (e.g. they may contain one or more asymmetric carbon atoms or may exhibit cis-trans isomerism). The individual stereoisomers (enantiomers and diastereomers) and mixtures of these are included within the scope of the present invention. The present invention also covers the individual isomers of the compounds represented by formula (I) as mixtures with isomers thereof in which one or more chiral centres are inverted. Likewise, it is understood that compounds of formula (I) may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention.

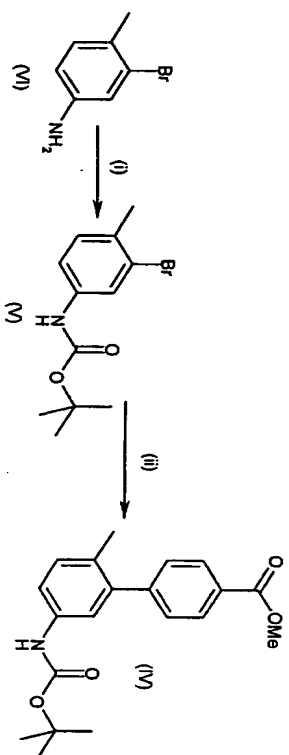
Salts of the compounds of the present invention are also encompassed within the scope of the invention and may, for example, comprise acid addition salts resulting from reaction of an acid with a nitrogen atom present in a compound of formula (I).

Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention. Representative salts include the following salts: Acetate, Benzenesulfonate, Benzoate, Bicarbonate, Bisulfate, Bitartrate, Borate, Bromide, Calcium Edetate, Camylate, Carboxylate, Chloride, Clavulanate, Citrate, Dihydrochloride, Edetate, Edisylate, Edoate, Etylate, Fumarate, Glucopate, Gluconate, Glutamate, Glycylglycylarsanilate, Hexyresorcinate, Hydrabamine, Hydrobromide, Hydrochloride, Hydroxynaphthoate, Iodide, Isethionate, Lactate, Lactobionate, Laurate, Malate, Maleate, Mandelate, Mesylate, Methylbromide, Methylglucamine, Oxalate, Pamotate (Embonate), Palmate, Panthothenate, Methylglucamine, Oxalate, Pamotate (Embonate), Palmate, Panthothenate, Phosphate/diphosphate, Polygalacturonate, Potassium, Salicylate, Sodium, Stearate, Subacetate, Succinate, Tannate, Tartate, Teoclate, Tosylate, Triethiodide, Trimethylammonium and Valerate. Other salts which are not pharmaceutically acceptable may be useful in the preparation of compounds of this invention and these form a further aspect of the invention.

The compounds of this invention may be made by a variety of methods, including standard chemistry. Any previously defined variable will continue to have the previously defined meaning unless otherwise indicated. Illustrative general synthetic methods are set out below and then specific compounds of the invention are prepared in the working Examples.

For example, a general method (A) for preparing the compounds of Formula (I) comprises the reactions set out in Scheme 1 below.

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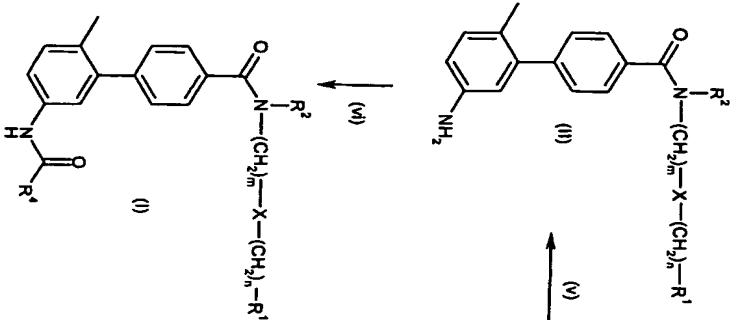
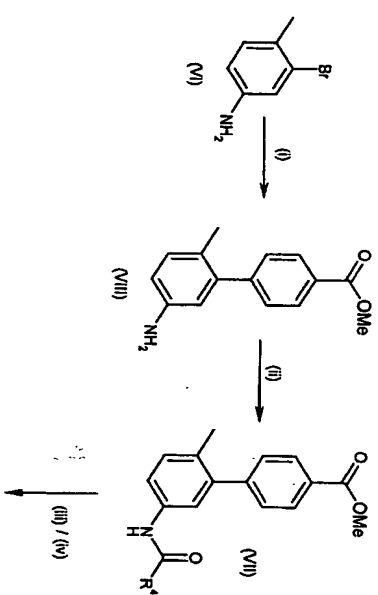


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- (i) Di-*t*-butyldicarbonate, Et₃N, DCM
 (ii) (4-Methoxycarbonylphenyl)boronic acid, (Ph₃P)₄Pd, CsCO₃, DME
 (iii) LiOH, THF, H₂O
 (iv) R¹(CH₂)_mX(CH₂)_nNR²H, HATU, DIPEA, THF
 (v) TFA, DCM
 (vi) R¹COOH, HATU, DIPEA, DMF

For example, a general method (B) for preparing the compounds of Formula (I) comprises the reactions set out in Scheme 2 below.

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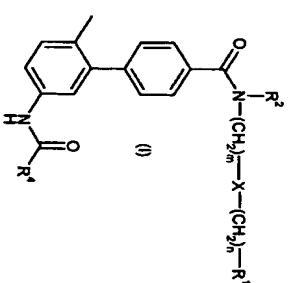


Scheme 1

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- (i) (4-Methoxycarbonylphenyl)boronic acid, (Ph₃P)₄Pd, CsCO₃, DME
 (ii) R¹COOH, HATU, DIPEA, DMF
 (iii) LiOH, THF, H₂O

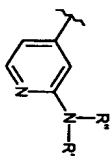
Scheme 2



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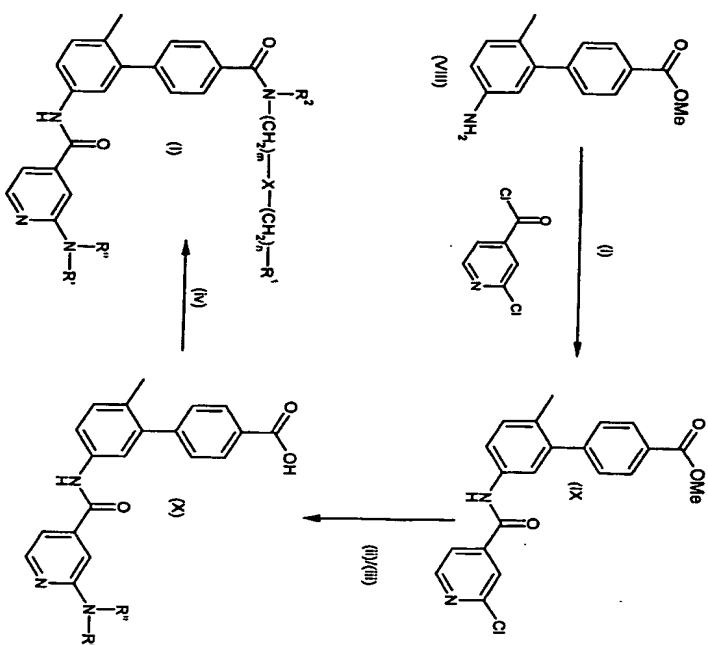
(iv) $R^1(CH_2)_mX(CH_2)_nR^2H$, HATU, DIPEA, THF

For example, a general method (C) for preparing the compounds of Formula (I) wherein R^4 is



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comprises the reactions set out in Scheme 3 below.



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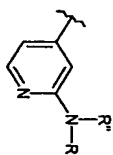
Scheme 3

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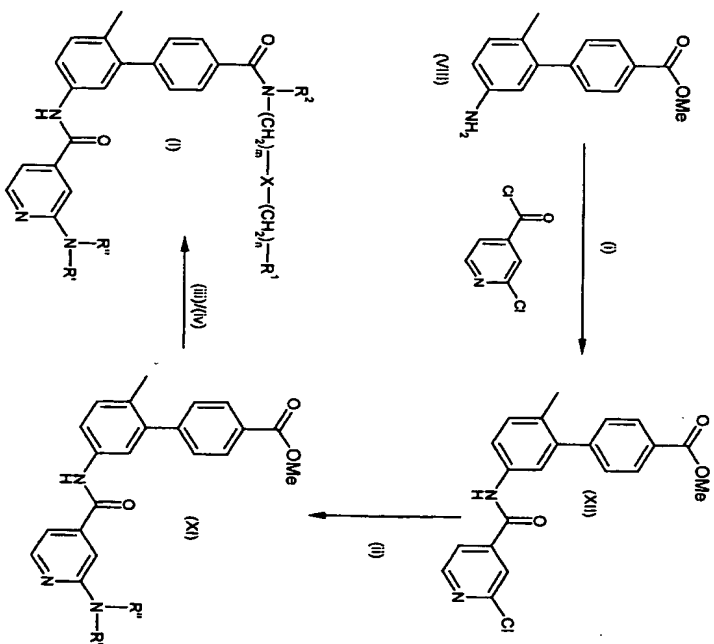
- (i) Et₃N, DCM
- (ii) LiOH, THF, H₂O
- (iii) R^1R^2NH
- (iv) $R^1(CH_2)_mX(CH_2)_nR^2H$, HATU, DIPEA, THF

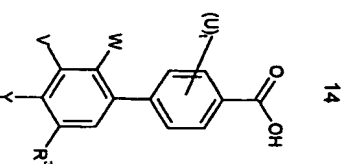
For example, a general method (D) for preparing the compounds of Formula (I) wherein R^4 is



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comprises the reactions set out in Scheme 4 below.





wherein R^3 , U, V, W, Y and I are as defined above,
with a compound of formula (XV)



(XV)

wherein R^1 , R^2 , X, m and n are as defined above,
under amide forming conditions.

Suitable amide forming conditions are well known in the art and include treating a solution of the acid, in for example THF, with an amine in the presence of, for example, HATU and DIPEA.

Whilst it is possible for the compounds, salts or solvates of the present invention to be administered as the new chemical, the compounds of formula (I) and their pharmaceutically acceptable salts and solvates are conveniently administered in the form of pharmaceutical compositions. Thus, in another aspect of the invention, we provide a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, in admixture with one or more pharmaceutically acceptable carriers, diluents or excipients.

The compounds of formula (I) and their pharmaceutically acceptable salts and solvates may be formulated for administration in any suitable manner. They may, for example, be formulated for topical administration or administration by inhalation or, more preferably, for oral, transdermal or parenteral administration. The pharmaceutical composition may be in a form such that it can effect controlled release of the compounds of formula (I) and their pharmaceutically acceptable salts and solvates. A particularly preferred method of administration, and corresponding formulation, is oral administration.

For oral administration, the pharmaceutical composition may take the form of, and be administered as, for example, tablets (including sub-lingual tablets) and capsules (each including timed release and sustained release formulations), pills,

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powders, granules, elixirs, tinctures, emulsions, solutions, syrups or suspensions prepared by conventional means with acceptable excipients.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing and coloring agent can also be present.

Capsules can be made by preparing a powder mixture as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an alginate, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or an absorption agent such as bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acacia mucilage or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material and a polish coating of wax can be

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provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives, flavor additives such as peppermint oil or saccharin, and the like can also be added.

Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax or the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds of the present invention can also be administered in the form of liposome emulsion delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, poly(hydroxypropylmethacrylamide-phenol, poly(hydroxyethylaspartamide-phenol, or poly(ethyleneoxide)polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polypeptide caprolactone, poly(hydroxy butyric acid, poly(orthoesters), polyacetals, poly(dihydropyrans, polycyanoacrylates and cross-linked or amphiphatic block copolymers of hydrogels.

The present invention includes pharmaceutical compositions containing 0.1 to 99.5%, more particularly, 0.5 to 90% of a compound of the formula (I) in combination with a pharmaceutically acceptable carrier.

Likewise, the composition may also be administered in nasal, ophthalmic, otic, rectal, topical, intravenous (both bolus and infusion), intraperitoneal, intraarticular, subcutaneous or intramuscular, inhalation or insufflation form, all using forms well known to those of ordinary skill in the pharmaceutical arts.

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For transdermal administration, the pharmaceutical composition may be given in the form of a transdermal patch, such as a transdermal iontophoretic patch.

For parenteral administration, the pharmaceutical composition may be given as an injection or a continuous infusion (e.g., intravenously, intravascularly or subcutaneously). The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. For administration by injection these may take the form of a unit dose presentation or as a multidose presentation preferably with an added preservative. Alternatively for parenteral administration the active ingredient may be in powder form for reconstitution with a suitable vehicle.

The compounds of the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

Alternatively the composition may be formulated for topical application, for example in the form of ointments, creams, lotions, eye ointments, eye drops, ear drops, mouthwash, impregnated dressings and sutures and aerosols, and may contain appropriate conventional additives, including, for example, preservatives, solvents to assist drug penetration, and emollients in ointments and creams. Such topical formulations may also contain compatible conventional carriers, for example cream or ointment bases, and ethanol or oily alcohol for lotions. Such carriers may constitute from about 1% to about 98% by weight of the formulation; more usually they will constitute up to about 80% by weight of the formulation.

For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, tetrafluoroethane, heptafluoropropane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g., gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

The pharmaceutical compositions generally are administered in an amount effective for treatment or prophylaxis of a specific condition or conditions. Initial dosing in human is accompanied by clinical monitoring of symptoms, such symptoms for the selected condition. In general, the compositions are administered in an amount of active agent of at least about 100 µg/kg body weight. In most cases they will be administered in one or more doses in an amount not in excess of about 20 mg/kg body weight per day. Preferably, in

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most cases, dose is from about 100 µg/kg to about 5 mg/kg body weight, daily. For administration particularly to mammals, and particularly humans, it is expected that the daily dosage level of the active agent will be from 0.1 mg/kg to 10 mg/kg and typically around 1 mg/kg. It will be appreciated that optimum dosage will be determined by standard methods for each treatment modality and indication, taking into account the indication, its severity, route of administration, complicating conditions and the like. The physician in any event will determine the actual dosage which will be most suitable for an individual and will vary with the age, weight and response of the particular individual. The effectiveness of a selected actual dose can readily be determined, for example, by measuring clinical symptoms or standard anti-inflammatory indicia after administration of the selected dose. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention. For conditions or disease states as are treated by the present invention, maintaining consistent daily levels in a subject over an extended period of time, e.g., in a maintenance regime, can be particularly beneficial.

In another aspect, the present invention provides a compound of formula (I) or a salt or solvate thereof, for use in therapy.

The compounds of the present invention are generally inhibitors of the serine/threonine kinase p38 and are therefore also inhibitors of cytokine production which is mediated by p38 kinase. Within the meaning of the term "inhibitors of the serine/threonine kinase p38" are included those compounds that interfere with the ability of p38 to transfer a phosphate group from ATP to a protein substrate according to the assay described below.

It will be appreciated that the compounds of the invention may be selective for one or more of the isoforms of p38, for example p38α, p38β, p38γ and/or p38δ. In one embodiment, the compounds of the invention selectively inhibit the p38α isoform. In another embodiment, the compounds of the invention selectively inhibit the p38β isoform. In a further embodiment, the compounds of the invention selectively inhibit the p38α and p38β isoforms. Assays for determining the selectivity of compounds for the p38 isoforms are described in, for example, WO 99/61426, WO 00/71535 and WO 02/46158.

It is known that p38 kinase activity can be elevated (locally or throughout the body). p38 kinase can be incorrectly temporally active or expressed, p38 kinase can be expressed or active in an inappropriate location, p38 kinase can be constitutively expressed, or p38 kinase expression can be erratic; similarly, cytokine production mediated by p38 kinase activity can be occurring at inappropriate times, inappropriate locations, or it can occur at detrimentally high levels.

Accordingly, the present invention provides a method for the treatment of a condition or disease state mediated by p38 kinase activity, or mediated by cytokines produced by the activity of p38 kinase, in a subject which comprises administering to

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said subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof. The compound may be administered as a single or polymorphic crystalline form or forms, an amorphous form, a single enantiomer, a racemic mixture, a single stereoisomer, a mixture of stereoisomers, a single diastereoisomer or a mixture of diastereoisomers.

The present invention also provides a method of inhibiting cytokine production which is mediated by p38 kinase activity in a subject, e.g., a human, which comprises administering to said subject in need of cytokine production inhibition a therapeutic, or cytokine-inhibiting, amount of a compound of the present invention. The compound may be administered as a single or polymorphic crystalline form or forms, an amorphous form, a single enantiomer, a racemic mixture, a single stereoisomer, a mixture of stereoisomers, a single diastereoisomer or a mixture of diastereoisomers.

The present invention treats these conditions by providing a therapeutically effective amount of a compound of this invention. By "therapeutically effective amount" is meant a symptom-alleviating or symptom-reducing amount, a cytokine-reducing amount, a cytokine-inhibiting amount, a kinase-regulating amount and/or a kinase-inhibiting amount of a compound. Such amounts can be readily determined by standard methods, such as by measuring cytokine levels or observing alleviation of clinical symptoms. For example, the clinician can monitor accepted measurement scores for anti-inflammatory treatments.

The compounds of the present invention can be administered to any subject in need of inhibition or regulation of p38 kinase or in need of inhibition or regulation of p38 mediated cytokine production. In particular, the compounds may be administered to mammals. Such mammals can include, for example, horses, cows, sheep, pigs, mice, dogs, cats, primates such as chimpanzees, gorillas, rhesus monkeys, and, most preferably, humans.

Thus, the present invention provides methods of treating or reducing symptoms in a human or animal subject suffering from, for example, rheumatoid arthritis, osteoarthritis, asthma, psoriasis, eczema, allergic rhinitis, allergic conjunctivitis, adult respiratory distress syndrome, chronic pulmonary inflammation, chronic obstructive pulmonary disease, chronic heart failure, silicosis, endotoxemia, toxic shock syndrome, inflammatory bowel disease, tuberculosis, atherosclerosis, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, epilepsy, multiple sclerosis, aneurism, stroke, irritable bowel syndrome, muscle degeneration, bone resorption diseases, osteoporosis, diabetes, reperfusion injury, graft vs. host reaction, allograft rejection, sepsis, systemic cachexia, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), malaria, leprosy, infectious arthritis, leishmaniasis, Lyme disease, glomerulonephritis, gout, psoriatic arthritis, Reiter's syndrome, traumatic arthritis, rubella arthritis, Crohn's disease, ulcerative colitis, acute synovitis, gouty arthritis, spondylitis,

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and non articular inflammatory conditions, for example, herniated/ruptured/prolapsed intervertebral disk syndrome, bursitis, tendonitis, tenosynovitis, fibromyalgic syndrome and other inflammatory conditions associated with ligamentous sprain and regional musculoskeletal strain, pain, for example that associated with inflammation and/or trauma, osteoporosis, restenosis, thrombosis, angiogenesis, cancer including breast cancer, colon cancer, lung cancer or prostatic cancer, which comprises administering to said subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

A further aspect of the invention provides a method of treatment of a human or animal subject suffering from rheumatoid arthritis, asthma, psoriasis, chronic pulmonary inflammation, chronic obstructive pulmonary disease, chronic heart failure, systemic cachexia, glomerulonephritis, Crohn's disease, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, epilepsy and cancer including breast cancer, colon cancer, lung cancer and prostatic cancer, which comprises administering to said subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

A further aspect of the invention provides a method of treatment of a human or animal subject suffering from rheumatoid arthritis, asthma, psoriasis, chronic pulmonary inflammation, chronic obstructive pulmonary disease, chronic heart failure, systemic cachexia, glomerulonephritis, Crohn's disease and cancer including breast cancer, colon cancer, lung cancer and prostatic cancer, which comprises administering to said subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

A further aspect of the invention provides a method of treatment of a human or animal subject suffering from rheumatoid arthritis, neurodegenerative disease, Alzheimer's disease, Parkinson's disease and epilepsy which comprises administering to said subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

A further aspect of the invention provides a method of treatment of a human or animal subject suffering from any type of pain including chronic pain, rapid onset of analgesis, neuromuscular pain, headache, cancer pain, acute and chronic inflammatory pain associated with osteoarthritis and rheumatoid arthritis, post operative inflammatory pain, neuropathic pain, diabetic neuropathy, trigeminal neuralgia, post-hepatic neuralgia, inflammatory neuropathies and migraine pain which comprises administering to said subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

A further aspect of the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the preparation of a medicament for the treatment of a condition or disease state mediated by p38 kinase activity or mediated by cytokines produced by p38 kinase activity.

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A further aspect of the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the preparation of a medicament for the treatment of a condition or disease state selected from rheumatoid arthritis, osteoarthritis, asthma, psoriasis, eczema, allergic rhinitis, allergic conjunctivitis, adult respiratory distress syndrome, chronic pulmonary inflammation, chronic obstructive pulmonary disease, chronic heart failure, silicosis, endotoxemia, toxic shock syndrome, inflammatory bowel disease, tuberculosis, atherosclerosis, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, epilepsy, multiple sclerosis, aneurism, stroke, irritable bowel syndrome, muscle degeneration, bone resorption diseases, osteoporosis, diabetes, reperfusion injury, graft vs. host reaction, allograft rejections, sepsis, systemic cachexia, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), malaria, leprosy, infectious arthritis, leishmaniasis, Lyme disease, glomerulonephritis, gout, psoriatic arthritis, Reiter's syndrome, traumatic arthritis, rubella arthritis, Crohn's disease, ulcerative colitis, acute synovitis, gouty arthritis, spondylitis, and non articular inflammatory conditions, for example, herniated/ruptured/prolapsed intervertebral disk syndrome, bursitis, tendonitis, tenosynovitis, fibromyalgic syndrome and other inflammatory conditions associated with ligamentous sprain and regional musculoskeletal strain, pain, for example that associated with inflammation and/or trauma, osteoporosis, restenosis, thrombosis, angiogenesis, and cancer including breast cancer, colon cancer, lung cancer or prostatic cancer.

A further aspect of the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the preparation of a medicament for the treatment of a condition or disease state selected from rheumatoid arthritis, asthma, psoriasis, chronic pulmonary inflammation, chronic obstructive pulmonary disease, chronic heart failure, systemic cachexia, glomerulonephritis, Crohn's disease, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, epilepsy, and cancer including breast cancer, colon cancer, lung cancer and prostatic cancer.

A further aspect of the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the preparation of a medicament for the treatment of a condition or disease state selected from rheumatoid arthritis, asthma, psoriasis, chronic pulmonary inflammation, chronic obstructive pulmonary disease, chronic heart failure, systemic cachexia, glomerulonephritis, Crohn's disease and cancer including breast cancer, colon cancer, lung cancer and prostatic cancer.

A further aspect of the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the preparation of a medicament for the treatment of a condition or disease state selected from rheumatoid

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arthritis, neurodegenerative disease, Alzheimer's disease, Parkinson's disease and epilepsy.

A further aspect of the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the preparation of a medicament for the treatment of any type of pain including chronic pain, rapid onset of analgesia, neuromuscular pain, headache, cancer pain, acute and chronic inflammatory pain associated with osteoarthritis and rheumatoid arthritis, post operative inflammatory pain, neuropathic pain, diabetic neuropathy, trigeminal neuralgia, post-hepatic neuralgia, inflammatory neuropathies and migraine pain.

The compounds of formula (I) and their salts, solvates and physiologically functional salts and solvates may be employed alone or in combination with other therapeutic agents for the treatment of the above-mentioned conditions. In particular, in rheumatoid arthritis therapy, combination with other chemotherapeutic or antibody agents is envisaged. Combination therapies according to the present invention thus comprise the administration of at least one compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof and at least one other pharmaceutically active agent. The compound(s) of formula (I) or pharmaceutically acceptable salt(s) or solvate(s) thereof and the other pharmaceutically active agent(s) may be administered together or separately and, when administered separately, this may occur separately or sequentially in any order. The amounts of the compound(s) of formula (I) or pharmaceutically acceptable salt(s) or solvate(s) thereof and the other pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect. Examples of other pharmaceutically active agents which may be employed in combination with compounds of formula (I) and their salts and solvates for rheumatoid arthritis therapy include: immunosuppressants such as azathioprine, cyclosporin, azathioprine, cyclosporin, cyclosporin A, hydroxychloroquine, azathioprine, azathioprine, gold sodium thiomalate and penicillamine.

Examples

The following examples are illustrative embodiments of the invention, not limiting the scope of the invention in any way. Reagents are commercially available or are prepared according to procedures in the literature.

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LCMS was conducted on a column (3.3cm x 4.6mm ID, 3µm ABZ-PLUS), at a Flow Rate of 3ml/min, Injection Volume of 5µl, at room temperature and UV Detection Range at 215 to 330nm.

Example 1: N-(6-Methyl-4-[(3-(4-methylpiperazin-1-yl)propylamino)carbonyl]-1,1'-biphenyl-3-yl)-2-pyrrolidin-1-ylisonicotinamide

a) 2-Methyl-5-[(2-pyrrolidin-1-ylisonicotinoyl)amino]-1,1'-biphenyl-4-carboxylic acid (40mg, 0.1mmol), HATU (38mg, 0.1mmol), HOBT (13mg, 0.1mmol), DIPEA (52µl), and 1-(3-aminomethyl)-4-methylpiperazine (19mg, 0.12mmol) were mixed in DMF (1ml) and stirred at room temperature for 18h. The solvent was evaporated under vacuum and the residue partitioned between DCM (5ml) and aqueous sodium carbonate (1M, 5ml). The organic phase was applied to a silica gel flash column and eluted with toluene/methanol (8:2, 7:3, 6:4), which after evaporation of the solvents under vacuum gave N-(6-methyl-4-[(3-(4-methylpiperazin-1-yl)propylamino)carbonyl]-1,1'-biphenyl-3-yl)-2-pyrrolidin-1-ylisonicotinamide (48mg, 89%). NMR: δ H (2H_g) - DMSO 10.51 (1H, s), 8.68 (1H, t), 8.17 (1H, d), 7.93 (2H, d), 7.76 (1H, dd), 7.72 (1H, d), 7.42 (2H, d), 7.28 (1H, d), 7.00 (1H, d), 6.95 (1H, d), 3.43 (4H, m), 3.29 (2H, q), 2.49-2.32 (10H, m), 2.21-2.18 (6H, m), 1.94 (4H, m), 1.70 (2H, m). LCMS: retention time 2.13min, MH⁺ 541.

b) 2-Methyl-5-[(2-pyrrolidin-1-ylisonicotinoyl)amino]-1,1'-biphenyl-4-carboxylic acid 5-[(2-Chloroisonicotinoyl)amino]-2-methyl-1,1'-biphenyl-4-carboxylic acid (600mg, 1.64mmol) and pyrrolidine (0.6ml) were heated in a sealed tube at 90°C for 5h. The excess pyrrolidine was evaporated under vacuum and the residue purified by flash chromatography (silica) eluting with DCM/methanol/monia (20:8:1). The solvents were evaporated under vacuum to give 2-methyl-5-[(2-pyrrolidin-1-ylisonicotinoyl)amino]-1,1'-biphenyl-4-carboxylic acid (546mg, 83%). LCMS: retention time 2.74min, MH⁺ 402.

c) 5-[(2-Chloroisonicotinoyl)amino]-2-methyl-1,1'-biphenyl-4-carboxylic acid Methyl 5-[(2-chloroisonicotinoyl)amino]-2-methyl-1,1'-biphenyl-4-carboxylate (1.63g, 4.28mmol) and lithium hydroxide monohydrate (376mg, 9.0mmol) were mixed in water (5ml) and THF (10ml) and stirred at room temperature for 90h. The pH was adjusted to pH3 by addition of hydrochloric acid (2N) and the mixture extracted with ethyl acetate (3x 50ml). The combined extracts were washed with water (75ml), brine (75ml), dried (magnesium sulphate) and concentrated under vacuum. The residue was purified by flash column chromatography on silica eluting with DCM/methanol/monia (30:8:1 then 20:8:1). The solvents were evaporated under vacuum to give 5-[(2-chloroisonicotinoyl)amino]-2-methyl-1,1'-biphenyl-4-carboxylic acid (1.15g, 73%). LCMS: retention time 3.53min, MH⁺ 367.

d) Methyl 5-[(2-chloroisonicotinoyl)amino]-2-methyl-1,1'-biphenyl-4-carboxylate

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- 2-Chloropyridine-4-carbonyl chloride (1.58g, 9.0mmol) in DCM (10ml) was added dropwise to a solution of methyl 5-amino-2-methyl-1,1'-biphenyl-4-carboxylate (1.81g, 7.5mmol) and triethylamine (3.13ml, 22.5mmol) in DCM (10ml) at 0°C. The reaction was stirred at room temperature for 20h, the solvent evaporated under vacuum and the residue partitioned between ethyl acetate (50ml) and saturated aqueous sodium bicarbonate (50ml). The aqueous was extracted with ethyl acetate (50ml) and the combined organic phases washed with brine (50ml), dried (magnesium sulphate) and the solvent evaporated under vacuum. The residue was purified by flash column chromatography on silica eluting with DCM/ethanol/monia (300:8:1). The solvents were evaporated under vacuum to give methyl 5-[(2-chloropyridin-1-yl)amino]-2-methyl-1,1'-biphenyl-4-carboxylate (1.73g, 61%). LCMS: retention time 3.69min, MH⁺ 381.

e) Methyl 5-amino-2-methyl-1,1'-biphenyl-4-carboxylate

- 3-Bromo-4-methylaniline (744mg, 4.0mmol), (4-methoxycarbonylphenyl)boronic acid (864mg, 4.8mmol), tetrakis(diphenylphosphine)palladium (100mg, 0.087mmol) and caesium carbonate (2.4g, 7.37mmol) were mixed in DME (30ml) and heated at 80°C for 20h. The reaction was absorbed onto silica applied to a silica SPE (10g) and eluted with ethyl acetate/cyclohexane (0-100% ethyl acetate). The solvent was evaporated from the product fractions under vacuum to give methyl 5-amino-2-methyl-1,1'-biphenyl-4-carboxylate (500mg, 43%). NMR: δ H CDCl₃ 8.07(2H, d), 7.38(2H, d), 7.07(1H, d), 6.87(1H, dd), 6.60(1H, d), 3.94(3H, s), 2.14(3H, s).

Example 2: N-(6-Methyl-4-[(3-morpholin-1-yl)propylamino]carbonyl)-1,1'-biphenyl-3-yl)-2-pyrrolidin-1-ylisonicotinamide

- 2-Methyl-5-[(2-pyrrolidin-1-yl)isonicotinoyl]aminol-1,1'-biphenyl-4-carboxylic acid (40mg, 0.1mmol), HATU (38mg, 0.1mmol), HOBT (13mg, 0.1mmol), DIPEA (52 μ l), and 3-morpholin-1-ylpropylamine (17mg, 0.12mmol) were mixed in DMF (1ml) and stirred at room temperature for 18h. The solvent was evaporated under vacuum and the residue partitioned between DCM (5ml) and aqueous sodium carbonate (1M, 5ml). The organic phase was applied to a silica gel flash column and eluted with toluene/methanol (8:2), which after evaporation of the solvents under vacuum gave N-(6-methyl-4-[(3-morpholin-1-yl)propylamino]carbonyl)-1,1'-biphenyl-3-yl)-2-pyrrolidin-1-ylisonicotinamide (18mg, 36%). NMR: δ H [2H₆] - DMSO 10.27(1H, s), 8.54(1H, t), 8.19(1H, d), 7.91(2H, d), 7.70(1H, dd), 7.65(1H, d), 7.44(2H, d), 7.29(1H, d), 6.96(1H, d), 6.85(1H, d), 3.56(4H, m), 3.43(4H, m), 3.31(2H, m), 2.34(6H, m), 2.20(3H, s), 1.95(4H, m), 1.69(2H, m). MS: MH⁺ 528.

Example 3: N-(4-[(3-imidazol-1-yl)propylamino]carbonyl)-6-methyl-1,1'-biphenyl-3-yl)-2-pyrrolidin-1-ylisonicotinamide

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- 2-Methyl-5-[(2-pyrrolidin-1-yl)isonicotinoyl]aminol-1,1'-biphenyl-4-carboxylic acid (40mg, 0.1mmol), HATU (38mg, 0.1mmol), HOBT (13mg, 0.1mmol), DIPEA (52 μ l), and 1-(3-anilino)pyrrolidin-1-ylisonicotinamide (15mg, 0.12mmol) were mixed in DMF (1ml) and stirred at room temperature for 18hours. The solvent was evaporated under vacuum and the residue partitioned between DCM (5ml) and aqueous sodium carbonate (1M, 5ml). The organic phase was applied to a silica gel flash column and eluted with toluene/methanol (8:2), which after evaporation of the solvents under vacuum gave N-(4-[(3-imidazol-1-yl)propylamino]carbonyl)-6-methyl-1,1'-biphenyl-3-yl)-2-pyrrolidin-1-ylisonicotinamide (12mg, 24%). NMR: δ H [2H₆] - DMSO 10.31(1H, s), 8.60(1H, t), 8.19(1H, d), 7.93(2H, d), 7.71(1H, dd), 7.67(2H, m), 7.45(2H, d), 7.30(1H, d), 7.22(1H, s), 6.96(1H, s), 6.86(1H, s), 4.03(2H, t), 3.43(4H, m), 3.26(2H, q), 2.20(3H, s), 1.99-1.93(6H, m). LCMS: retention time 2.24min, MH⁺ 509.

Example 4: N-(6-Methyl-4-[(4-methylpiperazin-1-yl)carbonyl]-1,1'-biphenyl-3-yl)-2-pyrrolidin-1-ylisonicotinamide

- 2-Methyl-5-[(2-pyrrolidin-1-yl)isonicotinoyl]aminol-1,1'-biphenyl-4-carboxylic acid (40mg, 0.1mmol), HATU (38mg, 0.1mmol), HOBT (13mg, 0.1mmol), DIPEA (52 μ l), and 1-methylpiperazine (15mg, 0.12mmol) were mixed in DMF (1ml) and stirred at room temperature for 18h. The solvent was evaporated under vacuum and the residue partitioned between DCM (5ml) and aqueous sodium carbonate (1M, 5ml). The organic phase was applied to a silica gel flash column and eluted with DCM/ethanol/monia (100:8:1 then 40:8:1), which after evaporation of the solvents under vacuum gave N-(6-methyl-4-[(4-methylpiperazin-1-yl)carbonyl]-1,1'-biphenyl-3-yl)-2-pyrrolidin-1-ylisonicotinamide (14mg, 29%). NMR: δ H [2H₆] - DMSO 10.26(1H, s), 8.19(1H, d), 7.69-7.67(2H, m), 7.47-7.41(4H, m), 7.29(1H, d), 6.96(1H, d), 6.86(1H, s), 3.59(2H, b), 3.43(4H, m), 2.33(6H, b), 2.21(3H, s), 2.21(3H, s), 1.95(4H, m). MS: MH⁺ 484.

Example 5: N-(4-[(3-4-Methylpiperazin-1-yl)propylamino]carbonyl)-6-methyl-1,1'-biphenyl-3-yl)-3-furamide

- a) 5-(3-Furoylamino)-2-methyl-1,1'-biphenyl-4-carboxylic acid (50mg, 0.156mmol), TBTV (60mg, 0.186mmol), 1-(3-aminopropyl)-4-methylpiperazine (25mg, 0.156mmol) and DIPEA (81 μ l, 0.467mmol) in DMF (1ml) were stirred at room temperature for 2h. The DMF was evaporated under vacuum and the residue dissolved in chloroform and filtered through an aminopropyl SPE (3g). The filtrate was purified by flash chromatography on silica, eluting with DCM/ethanol/monia (110:8:1), which after evaporation of the solvents under vacuum gave N-(4-[(3-4-methylpiperazin-1-yl)propylamino]carbonyl)-6-methyl-1,1'-biphenyl-3-yl)-3-furamide (12mg, 17%). NMR: δ H [2H₆] - DMSO 9.91(1H, s), 8.55(1H, t), 8.35(1H, s), 7.90(2H, d), 7.78(1H, t), 7.66(1H, dd), 7.59(1H, d), 7.43(2H, d), 7.27(1H, d), 6.98(1H, m), 3.28(2H, m), 2.46-

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2.20, (10H, m), 2.19, (3H, s), 2.13, (3H, s), 1.66, (2H, m). LCMS: retention time 2.37min, MH⁺ 461.

- 5 b) 5-(3-Furoylamino)-2-methyl-1,1'-biphenyl-4-carboxylic acid
Methyl 5-(3-furoylamino)-2-methyl-1,1'-biphenyl-4-carboxylate (980mg, 2.9mmol) and lithium hydroxide monohydrate (256mg, 6.1mmol) in THF (12ml) and water (6ml) were heated at 75°C for 18h. The THF was evaporated under vacuum and the aqueous adjusted to pH3 with hydrochloric acid (1M). The precipitate which formed was filtered off, washed with ether and dried under vacuum to give 5-(3-furoylamino)-2-methyl-1,1'-biphenyl-4-carboxylic acid (720mg, 77%). LCMS: retention time 3.33min, MH⁺ 322.

- 10 c) Methyl 5-(3-furoylamino)-2-methyl-1,1'-biphenyl-4-carboxylate
3-Furoic acid (557mg, 4.97mmol), HATU (1.89g, 4.97mmol), HBTU (560mg, 4.14mmol), methyl 5-amino-2-methyl-1,1'-biphenyl-4-carboxylate (1.0g, 4.14mmol) and DIPEA (2.17ml, 12.43mmol) were mixed in DMF (5ml) and the reaction stirred at room temperature for 18h. The DMF was evaporated under vacuum, the residue partitioned between DCM (50ml) and aqueous sodium carbonate (1M, 50ml) and the aqueous extracted with DCM (2x 30ml). The combined organics were washed with brine (75ml), dried (magnesium sulphate) and concentrated under vacuum. The residue was purified on a silica flash column eluting with DCM/methanol/ammonia (500:8:1), which after evaporation of the solvents under vacuum gave methyl 5-(3-furoylamino)-2-methyl-1,1'-biphenyl-4-carboxylate (800mg, 56%). LCMS: retention time 3.41min, MH⁺ 336.

25 Example 6: N-(6-Methyl-4-((3-morpholin-4-ylmethyl)benzyl)amino)carbonyl-1,1'-biphenyl-3-yl)-3-furamide

- a) 5-(3-Furoylamino)-2-methyl-1,1'-biphenyl-4-carboxylic acid (50mg, 0.156mmol), 3-(morpholin-4-ylmethyl)benzylamine (32mg, 0.156mmol), HATU (59.2mg, 0.156mmol), HOBT (21mg, 0.156mmol) and DIPEA (27μl, 0.156mmol) in DMF (2ml) were stirred at room temperature for 18h. The reaction was diluted with ethyl acetate (150ml), washed with water (2x 30ml) and dried (magnesium sulphate). The solvent was evaporated under vacuum and the residue chromatographed on a silica flash column eluting with DCM/methanol/triethylamine (98:2:2). Concentration of the product fractions under vacuum gave N-(6-methyl-4-((3-morpholin-4-ylmethyl)benzyl)amino)carbonyl-1,1'-biphenyl-3-yl)-3-furamide (51mg, 81%). NMR: δH [2H₆] - DMSO 9.92, (1H, s), 8.11, (1H, t), 8.35, (1H, s), 7.97, (2H, d), 7.78, (1H, t), 7.66, (1H, dd), 7.60, (1H, d), 7.46, (2H, d), 7.28, (3H, m), 7.22, (1H, d), 7.17, (1H, d), 6.98, (1H, m), 4.50, (2H, d), 3.54, (4H, m), 3.43, (2H, s), 2.33, (4H, m), 2.19, (3H, s). LCMS: retention time 2.40min, MH⁺ 510.

- 40 b) 5-(3-Furoylamino)-2-methyl-1,1'-biphenyl-4-carboxylic acid

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Methyl 5-(3-furoylamino)-2-methyl-1,1'-biphenyl-4-carboxylate (980mg, 2.9mmol) and lithium hydroxide monohydrate (256mg, 6.1mmol) in THF (12ml) and water (6ml) were heated at 75°C for 18h. The THF was evaporated under vacuum and the aqueous adjusted to pH3 with hydrochloric acid (1M). The precipitate which formed was filtered off, washed with ether and dried under vacuum to give 5-(3-furoylamino)-2-methyl-1,1'-biphenyl-4-carboxylic acid (720mg, 77%). LCMS: retention time 3.33min, MH⁺ 322.

- 5 c) Methyl 5-(3-furoylamino)-2-methyl-1,1'-biphenyl-4-carboxylate
3-Furoic acid (557mg, 4.97mmol), HATU (1.89g, 4.97mmol), HBTU (560mg, 4.14mmol), methyl 5-amino-2-methyl-1,1'-biphenyl-4-carboxylate (1.0g, 4.14mmol) and DIPEA (2.17ml, 12.43mmol) were mixed in DMF (5ml) and the reaction stirred at room temperature for 18h. The DMF was evaporated under vacuum, the residue partitioned between DCM (50ml) and aqueous sodium carbonate (1M, 50ml) and the aqueous extracted with DCM (2x 30ml). The combined organics were washed with brine (75ml), dried (magnesium sulphate) and concentrated under vacuum. The residue was purified on a silica flash column eluting with DCM/methanol/ammonia (500:8:1), which after evaporation of the solvents under vacuum gave methyl 5-(3-furoylamino)-2-methyl-1,1'-biphenyl-4-carboxylate (800mg, 56%). LCMS: retention time 3.41min, MH⁺ 336.

20 Example 7: N-(4-(((1-(4-butyloxy)carbonyl)piperidin-4-yl)methyl)amino)carbonyl)-6-methyl-1,1'-biphenyl-3-yl)-3-furamide

- 5-(3-Furoylamino)-2-methyl-1,1'-biphenyl-4-carboxylic acid (50mg, 0.156mmol), 1-(4-butyloxy)carbonyl-4-aminomethylpiperidine (33.3mg, 0.156mmol), HATU (59.2mg, 0.156mmol), HOBT (21mg, 0.156mmol) and DIPEA (27μl, 0.156mmol) in DMF (2ml) were stirred at room temperature for 18h. The reaction was diluted with ethyl acetate (150ml), washed with water (2x 30ml) and dried (magnesium sulphate). The solvent was evaporated under vacuum and the residue chromatographed on a silica flash column eluting with DCM/methanol/triethylamine (96:2:2). Concentration of the product fractions under vacuum N-(4-(((1-(4-butyloxy)carbonyl)piperidin-4-yl)methyl)amino)carbonyl)-6-methyl-1,1'-biphenyl-3-yl)-3-furamide (45mg, 56%). NMR: δH [2H₆] - DMSO 9.91, (1H, s), 8.56, (1H, t), 8.35, (1H, s), 7.91, (2H, d), 7.78, (1H, t), 7.66, (1H, dd), 7.59, (1H, d), 7.43, (2H, d), 7.27, (1H, d), 6.98, (1H, m), 3.93, (2H, m), 3.17, (2H, t), 2.68, (2H, b), 2.19, (3H, s), 1.74, (1H, b), 1.67, (2H, m), 1.38, (9H, s), 1.03, (2H, m). LCMS: retention time 3.50min, [MH-BOC]⁺ 418.

35 Example 8: N-(6-Methyl-4-((2-(4-methylpiperazin-1-yl)anilino)carbonyl)-1,1'-biphenyl-3-yl)-3-furamide

- 5-(3-Furoylamino)-2-methyl-1,1'-biphenyl-4-carboxylic acid (50mg, 0.156mmol), 2-(4-methylpiperazin-1-yl)aniline (29.8mg, 0.156mmol), HATU (59.2mg, 0.156mmol), HOBT (21mg, 0.156mmol) and DIPEA (27μl, 0.156mmol) in DMF (2ml) were stirred at room

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temperature for 18h. The reaction was diluted with ethyl acetate (150ml), washed with water (2x 30ml) and dried (magnesium sulphate). The solvent was evaporated under vacuum and the residue chromatographed on a silica flash column eluting with DCM/methanol/diethylamine (96:2:2). Concentration of the product fractions under vacuum N-(6-methyl-4-[(2-(4-methylpiperazin-1-yl)anilino)carbonyl]-1,1'-biphenyl-3-yl)-3-furamide (40mg, 52%). NMR: δ H [2H₆] – DMSO 9.93 (1H, s), 9.63 (1H, s), 8.35 (1H, s), 8.15 (1H, m), 8.02 (2H, d), 7.78 (1H, d), 7.68 (1H, dd), 7.65 (1H, d), 7.57 (2H, d), 7.31-7.27 (2H, m), 7.16-7.14 (2H, m), 6.98 (1H, m), 2.88 (4H, t), 2.51 (4H, m), 2.23 (6H, s). LCMS: retention time 2.68min, MH⁺ 495.

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Example 9: N-(6-Methyl-4-[(2-(4-methylpiperazin-1-ylmethyl)anilino)carbonyl]-1,1'-biphenyl-3-yl)-3-furamide

5-(3-Furoylamino)-2-methyl-1,1'-biphenyl-4-carboxylic acid (50mg, 0.156mmol), 2-(4-methylpiperazin-1-ylmethyl)aniline (32.0mg, 0.156mmol), HATU (59.2mg, 0.156mmol), HOBT (21mg, 0.156mmol) and DIPEA (27 μ l, 0.156mmol) in DMF (2ml) were stirred at room temperature for 18h. The reaction was diluted with ethyl acetate (150ml), washed with water (2x 30ml) and dried (magnesium sulphate). The solvent was evaporated under vacuum and the residue chromatographed on a silica flash column eluting with DCM/methanol/diethylamine (96:2:2). Concentration of the product fractions under vacuum N-(6-methyl-4-[(2-(4-methylpiperazin-1-ylmethyl)anilino)carbonyl]-1,1'-biphenyl-3-yl)-3-furamide (63mg, 79%). NMR: δ H [2H₆] – DMSO includes 11.56 (1H, s), 9.94 (1H, s), 8.38-8.34 (2H, m), 8.02 (2H, d), 7.78 (1H, d), 7.68 (1H, dd), 7.64 (1H, d), 7.54 (2H, d), 7.35-7.25 (3H, m), 7.06 (1H, m), 6.98 (1H, m), 3.73 (2H, s), 2.22 (3H, s), 2.11 (3H, s). LCMS: retention time 2.60min, MH⁺ 509.

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Example 10: N-(6-Methyl-4-[(3-(4-methylpiperazin-1-yl)anilino)carbonyl]-1,1'-biphenyl-3-yl)-3-furamide

5-(3-Furoylamino)-2-methyl-1,1'-biphenyl-4-carboxylic acid (50mg, 0.156mmol), 3-(4-methylpiperazin-1-yl)aniline (29.8mg, 0.156mmol), HATU (59.2mg, 0.156mmol), HOBT (21mg, 0.156mmol) and DIPEA (27 μ l, 0.156mmol) in DMF (2ml) were stirred at room temperature for 18h. The reaction was diluted with ethyl acetate (150ml), washed with water (2x 30ml) and dried (magnesium sulphate). The solvent was evaporated under vacuum and the residue chromatographed on a silica flash column eluting with DCM/methanol/diethylamine (96:2:2). Concentration of the product fractions under vacuum N-(6-methyl-4-[(3-(4-methylpiperazin-1-yl)anilino)carbonyl]-1,1'-biphenyl-3-yl)-3-furamide (59.5mg, 77%). NMR: δ H [2H₆] – DMSO 10.13 (1H, s), 9.93 (1H, s), 8.36 (1H, s), 8.02 (2H, d), 7.78 (1H, d), 7.68 (1H, dd), 7.63 (1H, d), 7.51 (2H, d), 7.43 (1H, m), 7.30-7.26 (2H, m), 7.17 (1H, t), 6.99 (1H, m), 6.70 (1H, dd), 3.12 (4H, m), 2.46 (4H, m), 2.22 (6H, s). LCMS: retention time 2.43min, MH⁺ 495.

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Example 11: N-(6-Methyl-4-[(2-(2-morpholin-4-ylethyl)anilino)carbonyl]-1,1'-biphenyl-3-yl)-3-furamide

a) 5-(3-Furoylamino)-2-methyl-1,1'-biphenyl-4-carboxylic acid (50mg, 0.156mmol), 2-(2-morpholin-4-ylethyl)aniline (32.2mg, 0.156mmol), HATU (59.2mg, 0.156mmol), HOBT (21mg, 0.156mmol) and DIPEA (27 μ l, 0.156mmol) in DMF (2ml) were stirred at room temperature for 18h. The reaction was diluted with ethyl acetate (150ml), washed with water (2x 30ml) and dried (magnesium sulphate). The solvent was evaporated under vacuum and the residue chromatographed on a silica flash column eluting with DCM/methanol/diethylamine (96:2:2). Concentration of the product fractions under vacuum N-(6-methyl-4-[(2-(2-morpholin-4-ylethyl)anilino)carbonyl]-1,1'-biphenyl-3-yl)-3-furamide (59.2mg, 74%). NMR: δ H [2H₆] – DMSO 10.08 (1H, s), 9.94 (1H, s), 8.36 (1H, s), 8.04 (2H, s), 7.79 (1H, t), 7.68 (1H, dd), 7.63 (1H, d), 7.52 (2H, d), 7.38-7.18 (4H, m), 6.98 (1H, m), 3.47 (4H, m), 2.80 (2H, t), 2.48 (2H, m), 2.34 (4H, m), 2.22 (3H, s). LCMS: retention time 2.60min, MH⁺ 510.

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b) 2-(2-Morpholin-4-ylethyl)aniline

4-[(2-Nitrophenyl)ethyl]morpholine (11.4g, 40mmol) and palladium on carbon (10%, 500mg) in ethanol (200ml) were hydrogenated under 1 atm. of hydrogen at room temperature for 3h. The reaction was filtered through hyflo and the filtrate reduced to dryness under vacuum. The residue was recrystallised from toluene/hexane to give 2-(2-morpholin-4-ylethyl)aniline (6.375g). Microanalysis: calculated C 69.87, H 8.80, N 13.56; found C 69.80, H 8.95, N 13.60.

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c) 4-[(2-Nitrophenyl)ethyl]morpholine

To a solution of 4-[(2-nitrophenyl)acetyl]morpholine (10g, 40mmol) in THF (250ml) was added borane-THF (1.0M, 60ml, 60mmol) and the mixture heated at reflux for 1h. A further portion of borane-THF (1.0M, 80ml, 80mmol) was added and reflux continued for 1h. The cooled reaction was quenched by addition of hydrochloric acid (concentrated, 8ml) and left at room temperature for 18h. The mixture was concentrated under vacuum, basified with aqueous sodium hydroxide (2N) and extracted with ether (3x 100ml). The combined extracts were dried (magnesium sulphate) and the solvent evaporated under vacuum to give a crude sample of 4-[(2-nitrophenyl)ethyl]morpholine (11.42g), which was used without further purification. Microanalysis: calculated C 61.007, H 6.83, N 11.86; found C 62.36, H 8.02, N 9.54.

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Example 12: N-(4-[(3-Imidazol-1-ylpropyl)amino]carbonyl-6-methyl-1,1'-biphenyl-3-yl)-3-furamide

5-(3-Furoylamino)-2-methyl-1,1'-biphenyl-4-carboxylic acid (50mg, 0.156mmol), 1-(3-aminopropyl)imidazole (19.5mg, 0.156mmol), HATU (59.2mg, 0.156mmol), HOBT (21mg, 0.156mmol) and DIPEA (27 μ l, 0.156mmol) in DMF (2ml) were stirred at room

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temperature for 18h. The reaction was diluted with ethyl acetate (150ml), washed with water (2x 30ml) and dried (magnesium sulphate). The solvent was evaporated under vacuum and the residue chromatographed on a silica flash column eluting with DCM/methanol/ethylamine (86:2:2). Concentration of the product fractions under vacuum N-(4'-[[[(3-imidazol-1-ylpropyl)amino]carbonyl]-6-methyl-1,1'-biphenyl-3-yl]-3-furanide (44.1mg, 66%). NMR: δ H [2 H₆] – DMSO 9.92 (1H, s), 8.58 (1H, t), 8.35 (1H, s), 7.82 (2H, d), 7.78 (1H, t), 7.67-7.65 (2H, m), 7.60 (1H, d), 7.44 (2H, d), 7.27 (1H, d), 7.22 (1H, m), 6.98 (1H, m), 6.89 (1H, m), 4.03 (2H, t), 3.26 (2H, q), 2.19 (3H, s), 1.97 (2H, m). LCMS: retention time 2.31min, MH⁺ 429.

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Example 13: N-(6-Methyl-4'-[[[(3-morpholin-4-ylpropyl)amino]carbonyl]-1,1'-biphenyl-3-yl]-3-furanide

5-(3-Furylamino)-2-methyl-1,1'-biphenyl-4-carboxylic acid (50mg, 0.156mmol), 4-(3-aminopropyl)morpholine (22.5mg, 0.156mmol), HATU (59.2mg, 0.156mmol), HOBT (21mg, 0.156mmol) and DIPEA (27 μ l, 0.156mmol) in DMF (2ml) were stirred at room temperature for 18h. The reaction was diluted with ethyl acetate (150ml), washed with water (2x 30ml) and dried (magnesium sulphate). The solvent was evaporated under vacuum and the residue chromatographed on a silica flash column eluting with DCM/methanol/ethylamine (86:2:2). Concentration of the product fractions under vacuum N-(6-methyl-4'-[[[(3-morpholin-4-ylpropyl)amino]carbonyl]-1,1'-biphenyl-3-yl]-3-furanide (59.5mg, 83%). NMR: δ H [2 H₆] – DMSO 8.94 (1H, s), 8.55 (1H, t), 8.36 (1H, s), 7.90 (2H, d), 7.78 (1H, t), 7.67 (1H, dd), 7.60 (1H, d), 7.43 (2H, d), 7.27 (1H, d), 6.98 (1H, m), 3.56 (4H, t), 3.30 (2H, m), 2.35-2.32 (6H, m), 2.19 (3H, s), 1.69 (2H, m). LCMS: retention time 2.42min, MH⁺ 448.

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Example 14: N-(6-Methyl-4'-[[[(4-methylpiperazin-1-yl)benzylamino]carbonyl]-1,1'-biphenyl-3-yl]thiophene-3-carboxamide

Example 15: N-(6-Methyl-4'-[[[(4-methylpiperazin-1-yl)methylthiophenyl]amino]carbonyl]-1,1'-biphenyl-3-yl]thiophene-3-carboxamide

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General Method A:

{3'-[(3-Thiophenylcarbonyl)amino]-6-methyl-1,1'-biphen-4-yl}carboxylic acid (intermediate 1, 40mg, 0.12mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (27mg, 0.14mmol), HOBT (19mg, 0.14mmol) and the appropriate amine (0.13mmol) were dissolved in DMF (5ml). DIPEA (25 μ l, 0.14mmol) was added to the solution which was then stirred for 16 hours at 20°C. The solvent was removed *in vacuo* and the residue was redissolved in ethyl acetate and washed with water. The

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ethyl acetate layer was separated, dried (magnesium), concentrated *in vacuo* and purified by mass-directed HPLC.

Compound	Amine	MH ⁺	Retention time (minutes)
Example 14	4-(4-methylpiperazin-1-yl)benzylamine	525	2.66
Example 15	3-(4-methylpiperazin-1-yl)methylphenylamine	525	2.71

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(a) {3'-[(3-Thiophenylcarbonyl)amino]-6-methyl-1,1'-biphen-4-yl}carboxylic acid (intermediate 1)

A solution of lithium hydroxide monohydrate (541mg, 12.9 mmol) in water (8ml) was added to a solution of methyl {3'-[(3-thiophenylcarbonyl)amino]-6-methyl-1,1'-biphen-4-yl}carboxylate (intermediate 2, 1.37g, 4.3mmol) in THF (10ml). The reaction was refluxed for 4 hours. Solvent was evaporated *in vacuo*, hydrochloric acid (0.5M, 50ml) was added and the product was extracted into ethyl acetate (2 x 50ml). The solvent was evaporated *in vacuo* to afford {3'-[(3-thiophenylcarbonyl)amino]-6-methyl-1,1'-biphen-4-yl}carboxylic acid (1.68g, 98%). NMR: δ H [2 H₆] – DMSO 13.10 (1H, bs), 8.33 (1H, dd), 8.03 (2H, d), 7.72 (1H, dd), 7.68-7.60 (3H, m), 7.50 (2H, d), 7.30 (1H, d), 2.20 (3H, s). LCMS: MH⁺ 338, retention time 3.47minutes.

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(b) Methyl {3'-[(3-thiophenylcarbonyl)amino]-6-methyl-1,1'-biphen-4-yl}carboxylate (intermediate 2)

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Methyl {3'-amino-6-methyl-1,1'-biphen-4-yl}carboxylate (1.45g, 6.0mmol), thiophene-3-carboxylic acid (0.846g, 6.6mmol), HOBT (0.973g, 7.2mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.38g, 7.2mmol) were dissolved in DMF (10ml). DIPEA (1.26ml, 7.2mmol) was added to the stirred solution, which was then stirred for 16 hours at 20°C. The solvent was removed *in vacuo* and the residue dissolved in ethyl acetate. The ethyl acetate solution was washed sequentially with aqueous sodium hydrogen carbonate (80ml) and hydrochloric acid (0.5M, 80ml), then dried (magnesium sulphate). The solvent was removed *in vacuo* and the residue was purified by silica biotage chromatography eluting with 4:1 cyclohexane:ethyl acetate. To give methyl {3'-[(3-thiophenylcarbonyl)amino]-6-methyl-1,1'-biphen-4-yl}carboxylate (1.78g, 84%).

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NMR: δ H (2 H₂) – DMSO 10.1 (1H, s), 8.33 (1H, m), 8.05 (2H, d), 7.72 (1H, dd), 7.70-7.60 (3H, m), 7.52 (2H, d), 7.30 (1H, d), 3.89 (3H, s), 2.20 (3H, s). LCMS: MH⁺ 352, retention time 3.64 minutes.

5 Example 16: N-[6-Methyl-4'-[(14-(4-methylpiperazin-1-yl)benzylamino)carbonyl]-1,1'-biphenyl-3-yl]isoxazole-3-carboxamide

Methyl (3'-[(3-isoxazoly)carbonyl]amino)-6'-methyl-1,1'-biphen-4-yl-carboxylate (intermediate 3, 640mg, 1.8mmol) was dissolved in THF (10ml) and a solution of lithium hydroxide monohydrate (252mg, 6.0mmol) in water (8ml) was added. The reaction was refluxed for 4 hours and then evaporated *in vacuo*. The residue was dissolved in DMF (4ml), HOBT (54mg, 0.4mmol), 1-(3-dimethylamino)propyl-3-ethylcarbodiimide hydrochloride (77mg, 0.4mmol) and DIPEA (70 μ l, 0.4mmol) were added. The mixture was stirred for 5 hours at 20°C. Water (40ml) and ethyl acetate (30ml) were added. After thorough mixing the ethyl acetate layer was separated. The water layer was extracted again with ethyl acetate (2 x 30ml). Ethyl acetate layers were combined, dried and evaporated *in vacuo*. The crude product was purified by mass-directed HPLC to yield N-[6-methyl-4'-[(14-(4-methylpiperazin-1-yl)benzylamino)carbonyl]-1,1'-biphenyl-3-yl]isoxazole-3-carboxamide (13mg, 1.5%)

20 NMR: δ H (2 H₂) – DMSO 10.7 (1H, s), 9.16 (1H, d), 9.00 (1H, b), 7.96 (2H, d), 7.72 (2H, dd+), 7.45 (2H, d), 7.30 (1H, d), 7.19 (2H, d), 6.90 (2H, d), 4.40 (2H, d), 3.10 (4H, m), 2.47 (4H, m), 2.22 (3H, s), 2.20 (3H, s). LCMS: MH⁺ 510, retention time 2.54 minutes.

25 (a) Methyl (3'-[(3-isoxazoly)carbonyl]amino)-6'-methyl-1,1'-biphen-4-yl-carboxylate (intermediate 3)

Methyl (3'-amino-6'-methyl-1,1'-biphen-4-yl)-carboxylate (0.483g, 2.0mmol), isoxazole-3-carboxylic acid (0.248g, 2.2mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.460g, 2.4mmol) and HOBT (0.324g, 2.4mmol) were dissolved in DMF (5ml). DIPEA (420 μ l, 2.4 mmol) was added to the solution, which was then stirred for 5 hours at 20°C. Ethyl acetate (50ml) and water (50ml) were added. The ethyl acetate layer was separated and washed sequentially with saturated sodium hydrogen carbonate (2 x 50ml) and hydrochloric acid (0.5M, 2 x 50ml), then dried (magnesium sulphate). The solvent was removed *in vacuo* to yield methyl (3'-[(3-isoxazoly)carbonyl]amino)-6'-methyl-1,1'-biphen-4-yl-carboxylate (650mg, 96%). LCMS: MH⁺ 337, retention time 3.42 minutes.

Example 17: N-[6-Methyl-4'-[(13-(morpholin-4-ylmethyl)benzylamino)carbonyl]-1,1'-biphenyl-3-yl]-3-furamide

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Example 18: tert-Butyl 4-[(15-(3-furoylamino)-2'-methyl-1,1'-biphenyl-4-yl)carbonyl]amino)methylpiperidine-1-carboxylate

Example 19: N-[6-Methyl-4'-[(12-(4-methylpiperazin-1-yl)phenylamino)carbonyl]-1,1'-biphenyl-3-yl]-3-furamide

5 Example 20: N-[6-Methyl-4'-[(12-(14-methylpiperazin-1-yl)methylpiperidin-1-yl)methyl]phenylamino)carbonyl]-1,1'-biphenyl-3-yl]-3-furamide

Example 21: N-[6-Methyl-4'-[(13-(4-methylpiperazin-1-yl)phenylamino)carbonyl]-1,1'-biphenyl-3-yl]-3-furamide

10 Example 22: N-[6-Methyl-4'-[(13-morpholin-4-yl)propylamino)carbonyl]-1,1'-biphenyl-3-yl]-3-furamide

Example 23: N-[4'-[(13-(1H-imidazol-1-yl)propylamino)carbonyl]-6-methyl-1,1'-biphenyl-3-yl]-3-furamide

General Method B:

15 [3-(3-Furoylamino)-6'-methyl-1,1'-biphen-4-yl]carboxylic acid (50mg), amine (0.155mmol), HATU (59.2mg), HOBT (21mg) and DIPEA (27 μ l) in DMF (2ml) were stirred for 18 hours at room temperature. The reaction was diluted with ethyl acetate (75ml), washed with water (2x 30ml), dried (magnesium sulphate) and reduced to dryness under vacuum. The residue was purified on a silica flash column (40g) eluting with DCM / methanol / triethylamine (95:5:2.5:2).

Compound	Amine	MH ⁺	Retention time (minutes)
Example 17	3-(4-morpholinylmethyl)-benzenemethanamine	510	2.40
Example 18	4-aminomethyl-N-(tert-butoxycarbonyl)piperidine	[MH-BOC] ⁺ 418	3.50
Example 19	2-(4-methyl-1-piperazinyl)aniline	495	2.68
Example 20	1-(2-aminobenzyl)-4-methylpiperazine	509	2.60
Example 21	3-(4-methyl-1-piperazinyl)aniline	495	2.43
Example 22	4-(3-aminopropyl)morpholine	448	2.42

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Example 23	1-(3-aminopropyl)imidazole	429	2.31
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Example 24: N-[4-((3-(1H-imidazol-1-yl)propyl)amino)carbonyl]-5-methyl-1'-biphenyl-3-ylthiophene-3-carboxamide

Example 25: tert-Buyl 4-((12-methyl-5-(thien-3-ylcarbonyl)amino)-1'-biphenyl-4-yl)carbonylamino)methyl)piperidine-1-carboxylate

Example 26: N-[6-Methyl-4-((3-morpholin-4-ylpropyl)amino)carbonyl]-1'-biphenyl-3-ylthiophene-3-carboxamide

Example 27: N-[6-Methyl-4-((3-(4-methylpiperazin-1-yl)propyl)amino)carbonyl]-1'-biphenyl-3-ylthiophene-3-carboxamide

Example 28: N-[6-Methyl-4-((12-(4-methylpiperazin-1-yl)ethyl)amino)carbonyl]-1'-biphenyl-3-ylthiophene-3-carboxamide

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General Method C:

{3-[(3-Thiophenylcarbonyl)amino]-6'-methyl-1'-biphen-4-yl}carboxylic acid (intermediate 1, 18mg, 0.06mmol), triethylamine (13ul) and 1-(methylsulphonyl)-1H-benzotriazole (12mg, 0.06mmol) were mixed in THF (0.5ml) and heated at reflux for 4 hours. The reaction was concentrated under vacuum and partitioned between chloroform (3ml) and water (2ml) and the organics reduced to dryness under vacuum. The residue was redissolved in THF (0.5ml) and was mixed with the amine (0.06mmol). After 20 hours the reaction was loaded onto an SPE (aminopropyl, 0.5g) and eluted with chloroform to give the desired product.

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Compound	Amine	MH+	Retention time (minutes)
Example 24	1-(3-aminopropyl)imidazole	445	2.43
Example 25	4-aminomethyl-N-(tert-butoxycarbonyl)piperidine	534	3.51
Example 26	4-(3-aminopropyl)morpholine	464	2.40
Example 27	1-(3-aminopropyl)-4-methylpiperazine	477	2.34
Example 28	1-(2-aminoethyl)-4-methylpiperazine	463	2.38

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Example 29: N-[6-Methyl-4-((3-(4-methylpiperazin-1-yl)phenyl)amino)carbonyl]-1'-biphenyl-3-ylisoxazole-5-carboxamide

{3-[(5-isoxazolylcarbonyl)amino]-6'-methyl-1'-biphen-4-yl}carboxylic acid (intermediate 4, 30mg), 3-(4-methyl-1-piperazinyl)aniline (17.8mg, HATU (35mg), HOBT (13mg) and DIPEA (48ul) in DMF (1ml) were stirred for 18 hours at room temperature. The reaction was purified by mass-directed autoprep to give N-[6-methyl-4-((3-(4-methylpiperazin-1-yl)phenyl)amino)carbonyl]-1'-biphenyl-3-ylisoxazole-5-carboxamide.

LCMS: MH⁺ 496, retention time 2.63 minutes.

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(a) {3-[(5-isoxazolylcarbonyl)amino]-6'-methyl-1'-biphen-4-yl}carboxylic acid (intermediate 4)

Methyl {3-[(5-isoxazolylcarbonyl)amino]-6'-methyl-1'-biphen-4-yl}carboxylate (intermediate 5, 2.84g), sulphuric acid (1M, 50ml) and ethanol (100ml) were heated at 75°C for 2 hours. The reaction was concentrated under vacuum and the resulting precipitate filtered off and washed with water. The resulting solid was purified on a flash silica column eluting with an ethyl acetate / cyclohexane gradient (33:66% ethyl acetate). Evaporation of the solvent under vacuum gave {3-[(5-isoxazolylcarbonyl)amino]-6'-methyl-1'-biphen-4-yl}carboxylic acid.

LCMS: MNH⁺ 340, retention time 3.11 minutes.

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(b) Methyl {3-[(5-isoxazolylcarbonyl)amino]-6'-methyl-1'-biphen-4-yl}carboxylate (intermediate 5)

Methyl {3'-amino-6'-methyl-1'-biphen-4-yl}carboxylate (2g), HATU (3.16g), DIPEA (4.32ml), 5-isoxazolecarboxylic acid (0.95g) in DMF (30ml) and ethyl acetate (50ml) were stirred at room temperature for 2 hours. The reaction was diluted with ethyl acetate (500ml), washed with hydrochloric acid (0.5M, 2x 200ml), aqueous sodium hydrogen carbonate (2x 200ml) and dried (magnesium sulphate). The solvent was evaporated in vacuo to give methyl {3-[(5-isoxazolylcarbonyl)amino]-6'-methyl-1'-biphen-4-yl}carboxylate.

LCMS: [M-H]⁺ 335, retention time 3.17 minutes.

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Abbreviations

DCM	Dichloromethane
DIPEA	N,N-Diisopropylethylamine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethylsulphoxide

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HATU	O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HBTU	O-Benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate
HOBT	1-Hydroxybenzotriazole hydrate
PyBOP	Benzotriazol-1-yl-l-oxy-triisopropylidiphosphonium hexafluorophosphate
SPE	Solid phase extraction
THF	Tetrahydrofuran

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described herein. They may take the form of product, composition, process or use claims and may include, by way of example and without limitation, one or more of the following claims:

10 The activity of the compounds of the invention as p38 inhibitors may be demonstrated in the following assays:

p38 Kinase Assay

15 The peptide substrate used in the p38 assay was biotin-IPSPITTTTFFRRR-amide. The p38 and MEK6 proteins were purified to homogeneity from E.coli expression systems. The fusion proteins were tagged at the N-terminus with Glutathione-S-Transferase (GST). The maximum activation was achieved by incubating 20uL of a reaction mixture of 30nM MEK6 protein and 120nM p38 protein in the presence of 1.5uM peptide and 10mM Mg(CH₃CO₂)₂ in 100mM HEPES, pH 7.5, added to 15uL of a mixture of 1.5uM ATP with 0.08uCi [γ-³²P]ATP, with or without 15uL of inhibitor in 6% DMSO. The controls were reactions in the presence (negative controls) or absence (positive controls) of 50 mM EDTA. Reactions were allowed to proceed for 20 60 min at room temperature and quenched with addition of 50uL of 250mM EDTA and mixed with 150uL of Streptavidin SPA beads (Amersham) to 0.5mg/reaction. The Dynatech Microfluor white U-bottom plates were sealed and the beads were allowed to settle overnight. The plates were counted in a Packard TopCount for 60 seconds. IC₅₀ values were obtained by fitting raw data to %I = 100*(1-(C2)/(C1-C2)), where I was CPM of background, C1 was positive control, and C2 was negative control.

30 α P38 Fluorescence Polarisation Method

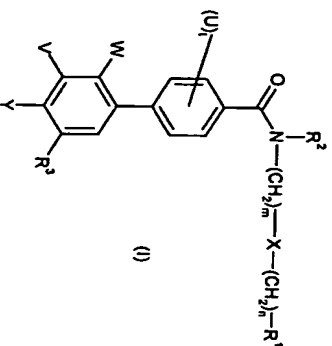
α P38 was prepared in house. SB4777790-R Ligand was diluted in HEPES containing MgCl₂, CHAPS, DTT and DMSO. This was added to blank wells of a Black NUNC 384 well plate. α P38 was added to this ligand mixture then added to the remainder of the 384 well plate containing controls and compounds. The plates were 35 read on an LLI Analyst and Fluorescence Anisotropy used to calculate the compound inhibition.

40 The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features

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Claims:

1. A compound of formula (I):



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wherein

X is a bond or a phenyl group which may be optionally substituted.

- 10 R^1 is selected from an optionally substituted five- to seven-membered heterocyclic ring, an optionally substituted five- to seven-membered heteroaryl ring and an optionally substituted fused bicyclic ring.

R^2 is selected from hydrogen, C_{1-6} alkyl and $-(CH_2)_6-C_{3-7}$ cycloalkyl;

- 15 or when X is a bond and m and n are both zero, R^1 and R^2 , together with the nitrogen atom to which they are bound, form a five- to six-membered heterocyclic ring optionally containing up to one additional heteroatom selected from oxygen and nitrogen, which can be optionally substituted by C_{1-6} alkyl

R^3 is the group $-NH-CO-R^4$.

- 20 R^4 is selected from hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, $-(CH_2)_6-C_{3-7}$ cycloalkyl, trifluoromethyl, $-(CH_2)_6$ phenyl optionally substituted by R^5 and/or R^6 , $-(CH_2)_6$ heteroaryl optionally substituted by R^6 and/or R^6 , $-(CH_2)_6$ heterocyclo optionally substituted by R^5 and/or R^6 and/or R^6 and $-(CH_2)_6$ fused bicycyl optionally substituted by R^5 and/or R^6 .

- 25 R^5 is selected from C_{1-6} alkyl, C_{1-6} alkoxy, $-(CH_2)_6-C_{3-7}$ cycloalkyl, $-CONR^7R^8$, $-NHCOR^8$, $-SO_2NHR^7$, $-NHCO_2R^8$, halogen, $-(CH_2)_6NR^7R^8$, oxy, trifluoromethyl, phenyl optionally substituted by one or more R^6 groups and heteroaryl wherein the heteroaryl may be optionally substituted by one or more R^6 groups.

- R^6 is selected from C_{1-6} alkyl, C_{1-6} alkoxy, halogen, trifluoromethyl and $-NR^7R^8$, or R^7 and R^8 , together with the carbon atoms to which they are bound, form a five- or six-membered saturated or unsaturated ring to give a fused bicyclic ring system, wherein the ring that is formed by R^5 and R^6 may optionally contain one or two heteroatoms selected from oxygen, nitrogen and sulfur.

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R^7 is selected from hydrogen, C_{1-6} alkyl and phenyl wherein the phenyl group may be optionally substituted by one or more R^6 groups.

R^8 is selected from hydrogen and C_{1-6} alkyl;

5 or R^7 and R^8 , together with the nitrogen atom to which they are bound, form a five- to six-membered heterocyclic ring optionally containing one additional heteroatom selected from oxygen, sulfur and N- R^7 , wherein the ring may be substituted by up to two C_{1-6} alkyl groups.

R^9 is selected from hydrogen and methyl;

- 10 R^9 is selected from hydrogen, C_{1-6} alkyl and $-(CH_2)_6-C_{3-7}$ cycloalkyl optionally substituted by C_{1-6} alkyl;

R^{10} is selected from hydrogen and C_{1-6} alkyl;

- 15 or R^9 and R^{10} , together with the nitrogen atom to which they are bound, form a three- to seven-membered heterocyclic ring optionally containing one additional heteroatom selected from oxygen, sulfur and nitrogen, wherein the ring may contain up to one double bond and the ring may be substituted by one or more R^{11} groups.

R^{11} is selected from C_{1-6} alkyl, oxy, $-CH_2OC_{1-6}$ alkyl, trichloromethyl and $-N(C_{1-6}alkyl)_2$.

U is selected from methyl and halogen.

W is selected from methyl and chlorine.

V and Y are each selected independently from hydrogen, methyl and halogen;

m and n are independently selected from 0, 1 and 2, wherein each carbon atom

of the resulting carbon chain may be optionally substituted with up to two groups selected independently from C_{1-6} alkyl and the sum of m + n is from 0 to 4;

p, q and r are independently 0 or 1;

s is 0, 1, 2 or 3;

t is selected from 0, 1 and 2;

or a pharmaceutically acceptable salt or solvate thereof.

- 20 2. A compound according to claim 1 wherein R^1 is optionally substituted by up to three substituents selected from C_{1-6} alkyl, C_{1-6} alkoxy, oxy, halogen, hydroxy C_{1-6} alkyl, $-N(C_{1-6}alkyl)_2$, $-CH_2-N(C_{1-6}alkyl)_2$, $-CO_2C_{1-6}alkyl$, phenyl optionally substituted by halogen and benzyl optionally substituted by halogen and/or cyano.

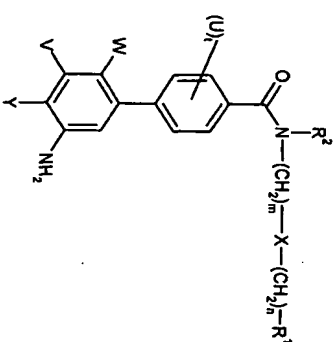
- 35 3. A compound according to claim 1 or 2 wherein X is optionally substituted phenyl, and R^1 is selected from optionally substituted pyrrolidinyl, furyl, pyrrolyl, imidazolyl, imidazolidinyl, pyrazolyl, tetrazolyl, oxazolyl, oxadiazolyl, piperidinyl, piperazinyl, morpholino, pyridyl, pyrimidinyl, thienyl, benzimidazolyl and quinolyl; wherein the optional substituents for R^1 are selected independently from C_{1-6} alkyl, C_{1-6} alkoxy, oxy, halogen, hydroxy C_{1-6} alkyl, $-N(C_{1-6}alkyl)_2$ and $-CH_2-N(C_{1-6}alkyl)_2$.

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4. A compound according to claim 1 or 2 wherein X is a bond, and R¹ is selected from an optionally substituted pyrrolidinyl, isoxazolyl, furyl, thienyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, thiazolyl, oxadiazolyl, piperidinyl, piperazinyl, morpholino, pyrrolyl, tetrahydrofuranyl, tetrahydrothiophenyl and quinolyl; wherein the optional substituents for R¹ are selected independently from C₁₋₆alkyl, C₁₋₆alkoxy, oxy, halogen, hydroxyc₁₋₆alkyl, -N(C₁₋₆alkyl)₂, -CH₂-N(C₁₋₆alkyl)₂, -CO₂C₁₋₆alkyl, phenyl optionally substituted by halogen and benzyl optionally substituted by halogen and/or cyano.
5. A compound according to any one of the preceding claims wherein R² is selected from hydrogen, C₁₋₆alkyl and -CH₂-cyclopropyl.
6. A compound according to any one of the preceding claims wherein R⁴ is selected from -(CH₂)_nphenyl optionally substituted by R⁵ and/or R⁶ and -(CH₂)_nheteroaryl optionally substituted by R⁵ and/or R⁶.
7. A compound according to claim 6 wherein R⁴ is -(CH₂)_nheteroaryl optionally substituted by R⁵ and/or R⁶.
8. A compound according to any one of the preceding claims wherein m and n are independently selected from 0, 1 and 2, and the sum of m+n is from 0-3.
9. A compound according to claim 1 as defined in any one of Examples 1 to 29, or a pharmaceutically acceptable salt or solvate thereof.
10. A process for preparing a compound according to any one of claims 1 to 9 which comprises:
 - (a) reacting a compound of formula (XII)

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(XII)

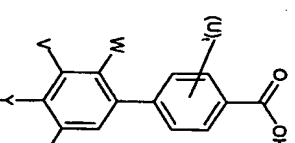
- 5 wherein R¹, R², U, V, W, X, Y, m, n and t are as defined in claim 1, with a compound of formula (XIII)



(XIII)

- 10 wherein R⁴ is as defined in claim 1, under amide forming conditions, optionally converting the acid compound (XIII) to an activated form of the acid before reaction with the amine compound (XII), or

- (b) reacting a compound of formula (XIV)



(XIV)

- 15 wherein R³, U, V, W, Y and t are as defined in claim 1, with a compound of formula (XV)



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wherein R¹, R², X, m and n are as defined in claim 1,
under amide forming conditions.

(XV)

11. A pharmaceutical composition comprising a compound according to any one of claims 1 to 9 or a pharmaceutically acceptable salt or solvate thereof, in admixture with one or more pharmaceutically acceptable carriers, diluents or excipients.

12. A method for treating a condition or disease state mediated by p38 kinase activity or mediated by cytokines produced by the activity of p38 kinase comprising administering to a patient in need thereof a compound according to any one of claims 1 to 9 or a pharmaceutically acceptable salt or solvate thereof.

13. A compound according to any one of claims 1 to 9 or a pharmaceutically acceptable salt or solvate thereof for use in therapy.

14. Use of a compound according to any one of claims 1 to 9 or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for use in the treatment of a condition or disease state mediated by p38 kinase activity or mediated by cytokines produced by the activity of p38 kinase.

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07D295/12 C07D233/64 C07D295/18 C07D307/68 C07D333/38 C07D261/18 A61K31/415 A61K31/44 A61K31/495 A61P29/00		
According to International Patent Classification (IPC) or to both national classification and IPC		
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, WPI Data, PAJ, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	NO 00 71535 A (SCIOS INC) 30 November 2000 (2000-11-30) cited in the application claims, examples	1, 10-14
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Date of the actual completion of the international search 5 March 2003		Date of mailing of the international search report 14/03/2003
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